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Trait anxiety affects decision-making differently in healthy men and women: Towards gender-specific endophenotypes of anxiety

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ABSTRACT

Excessive levels of trait anxiety are a risk factor for psychiatric conditions, including anxiety disorders and substance abuse. High trait anxiety has been associated with altered cognitive functioning, in particular with an attentional bias towards aversive stimuli. Decision-making is a crucial aspect of cognitive functioning that relies on the correct processing and control of emotional stimuli. Interestingly, anxiety and decision-making share underlying neural substrates, involving cortico-limbic pathways, including the amygdala, striatum and medial and dorsolateral prefrontal cortices. In the present study, we investigated the relationship between trait anxiety, measured by the State-Trait Anxiety Inventory, and complex decision-making, measured by the Iowa Gambling Task, in healthy male and female volunteers. The main focus of this study was the inclusion of gender as a discriminative factor. Indeed, we found distinct gender-specific effects of trait anxiety: in men, both low and high anxiety groups showed impaired decision-making compared to medium anxiety individuals, whereas in women only high anxiety individuals performed poorly. Furthermore, anxiety affected decision-making in men early in the task, i.e. the exploration phase, as opposed to an effect on performance in women during the second part of the test, i.e. the exploitation phase. These findings were related to different profiles of trait anxiety in men and women, and were independent of performance in the Wisconsin Card Sorting Test and cortisol levels. Our data show gender-specific effects of trait anxiety on emotional decision-making. We suggest gender-specific endophenotypes of anxiety to exist, that differentially affect cognitive functioning.

1. Introduction

Anxiety is an adaptive emotion, aimed at adequately directing an individual's response towards a possible threatening stimulus or situation. In its exaggerated form, however, anxiety may develop into a psychiatric disorder with detrimental consequences for the quality of life. In fact, on the Disability-Adjusted Life-Years scale, anxiety disorders appear among severe somatic diseases such as coronary artery disease and stroke (RIVM, 2009). In the US and Europe, anxiety disorders have a high prevalence, i.e. 15–20% of the population suffer from an anxiety disorder in a given year (Alonso et al., 2004; Kessler, Chiu, Demler, & Walters, 2005; NIMH, 2008). The trajectory from normal to pathological forms of anxiety is suggested to be a continuum: individuals with high levels of anxiety disposition, i.e. trait anxiety (TA), are at risk for developing one or more of the anxiety disorders as defined by the DSM-IV (Bennet & Stirling, 1998; Mathews & MacLeod, 2005). High TA is also associated with increased risk for substance abuse and depression (NIMH, 2008; Willinger et al., 2002).

Anxiety exerts its influence on cognitive functioning by altering the processing of environmental information in favour of stimuli that are negative in affect, resulting in attentional, memory and interpretative biases towards such stimuli (Barlow, 2002; Bishop, Duncan, Brett, & Lawrence, 2004; Calvo, Avero, & Miguel-Tobal, 2003; Mathews, 1990; Mathews & Mackintosh, 1998). An essential aspect of cognitive functioning that relies on the correct labelling, processing and control of emotional stimuli is decision-making. Decision-making involves the integration of information about options that vary in both long- and short-term costs and benefits, ultimately converging into a successful choice strategy. Disruption of decision-making processes leads to problems in many different areas, such as in social and financial affairs (Bechara, Damasio, Damasio, & Anderson, 1994). A frequently used task to measure decision-making in the laboratory environment is the Iowa Gambling Task (IGT; Bechara et al., 1994; Bechara, Damasio, Damasio, & Lee, 1999). The IGT models the daily life development of long-term profitable strategies as participants have to choose between

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four decks of cards that differ in the frequency and magnitude of monetary gains and losses and are either advantageous or disadvantageous in the long run. As the task progresses, healthy participants shift from exploration of the different options, in order to obtain information about the most profitable decks, to exploitation of the once established choice (Bechara et al., 1994, 1999; Homberg, Van den Bos, Den Heijer, Suer, & Cuppen, 2008; Van den Bos, den Heijer, Vlaar, & Houx, 2007; Van den Bos, Harteveld, & Stoop, 2009). A crucial aspect that sets the IGT aside from other tests of decision-making is the uncertainty of the outcome of each option as all options contain both unexpected gains and losses. Several neural substrates have been identified and suggested to underlie this real-life form of decision-making: the orbitofrontal cortex (OFC), amygdala (AMY) and ventral striatum (vSTR) are thought to mediate the exploration phase of the task, whereas the exploitation phase is suggested to be regulated by the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (dlPFC) and the dorsal striatum (dSTR) (Bechara et al., 1999; Bolla, Eldreth, Matochik, & Cadet, 2004; Brand, Labudda, & Markowitsch, 2006; Doya, 2008; Ernst et al., 2002; Van den Bos, Houx, & Spruijt, 2006; Van den Bos et al., 2007).

Several of the neural substrates involved in decision-making also play a major role in anxiety: high anxiety has been associated with enhanced amygdala and vmPFC activation (Etkin et al., 2004; Grachev & Apkarian, 2000; Simpson, Drevets, Snyder, Gusnard, & Raichle, 2001) and changed activity of the ACC (Bishop et al., 2004; Bishop, 2008; Paulus, Feinstein, Simmons, & Stein, 2004) and of the dlPFC (Bishop et al., 2004; Bishop, 2008). Thus, anxiety may affect decision-making at the level of both emotional reactivity, involving the AMY, vSTR and OFC, and cognitive control, involving the ACC, dlPFC and dSTR. Indeed, Miu, Heilman, and Houser (2008) recently reported that high trait anxiety individuals show an impaired performance on the IGT.

Interestingly, gender differences have been reported separately for anxiety and decision-making: women display higher levels of trait anxiety than men and are more vulnerable to develop anxiety disorders (Alonso et al., 2004; McCleary & Zucker, 1991). On decision-making in the IGT, men outperform women and show a more goal-directed choice pattern (Van den Bos et al., 2007; Van den Bos, Harteveld, et al., 2009; Reavis & Overman, 2001). Moreover, differences in performance on the IGT between men and women are related to differences in dorsolateral PFC activation (Bolla et al., 2004). Therefore, it is crucial to take gender as an important discriminative factor into account when studying the interaction between anxiety and decision-making and its underlying neural substrates. Accordingly in the present study, we aim to further establish the intricate relationship between trait anxiety and decision-making and extend earlier findings (Miu et al., 2008) by addressing gender-specific effects.

Here we therefore classified healthy male and female volunteers on the State-Trait Anxiety Inventory (STAI: Spielberger, 1983; Van der Ploeg, 2000) and related their scores to their performance on the IGT to elucidate gender-specific interactions between anxiety and decision-making. We included an in-depth analysis of STAI items in relation to gender using principal component analysis, and of the IGT using the expectancy-valence model (Busemeyer & Stout, 2002). To control for differences in executive functioning – known to influence performance on the IGT (Bechara, Damasio, & Damasio, 2000; Preston, Buchanan, Stansfield, & Bechara, 2007; Van den Bos, Harteveld, et al., 2009) – participants performed the Wisconsin card sorting test (Heaton, Chelune, Talley, Kay, & Curtis, 1993). Furthermore, heightened stress in high TA subjects was suggested as a possible confounding factor underlying the interaction between TA and decision-making (Miu et al., 2008). We therefore controlled for potential differences in stress related to state-dependent factors on the day of testing among TA groups by obtaining pre- and post-task salivary cortisol samples.

2. Materials and methods

2.1. Participants

Men ($n = 65$, mean age ± SEM = 22.4 ± 0.6 years) and women ($n = 43$, mean age ± SEM = 20.8 ± 0.7 years) were recruited at Utrecht University Campus. They all received €6 for participating and a lottery ticket for winning €50, which was held when all subjects had been tested. Participants had normal weight according to their BMI (body mass index: male subjects, mean ± SEM = 23.0 ± 0.7; female subjects, mean ± SEM = 21.8 ± 0.8) no history of or current psychological disorders or past or present use of drugs or medication, determined by a questionnaire. As it proved difficult to recruit solely female subjects in this age-class at the university campus who did not use oral contraceptives, we decided to also include subjects taking oral contraceptives. The use of oral contraceptives was found to have no effect on IGT performance and salivary cortisol levels in our hands (Van den Bos, Harteveld, et al., 2009). We did not control for the menstrual cycle as it is has been shown not to interfere with IGT performance (Reavis & Overman, 2001; Van den Bos et al., 2007), nor with levels of trait anxiety (Contreras, Marván, Alcalá-Herrera, & Yeyha, 1989; Golub & Harrington, 1981). The study was performed in accordance with the ethical standards as formulated in the 1964 Declaration of Helsinki.

2.2. Experimental procedure

Testing was conducted between 09:00 and 18:00 h. When entering the experimental room the procedure was explained and all subjects signed an informed consent, which stated that participation was out of free will and leaving the experiment was possible at all times during the study. Subsequently, a questionnaire was requested to be filled in, followed by a 15-min period in which the subjects were left alone and were allowed to read magazines while music was played (George Winston, December, 1984, Windham Hill Records; see Van den Bos, Harteveld, et al., 2009). Thereafter, the first saliva cortisol sample was taken, followed by completion of the State Trait Anxiety Inventory (STAI) questionnaire. Next, all subjects performed the IGT. When having completed the task, saliva was sampled using a vial (Oragene-DNA, DNAGenotek Inc., Kanata, Ontario, Canada) for later genotype determination, of which the results will not be discussed in this paper. Lastly, subjects were requested to perform the Wisconsin Card Sorting Test, followed by the last saliva cortisol sample.

2.3. State Trait Anxiety Inventory (STAI)

The STAI questionnaire (Spielberger, 1983) allows determination of both state anxiety and trait anxiety. Given the Dutch nationality of all participants, we used the Dutch version of the STAI (Van der Ploeg, 2000). The form is comprised of two sides, each side containing 20 statements ("items"). One side includes 20 items concerning how the subjects feel at the time the questionnaire was filled in (state anxiety, SA), whereas on the other side, the subjects have to indicate how they feel in general (trait anxiety, TA), both on a 4-point scale. For the present study, we were mainly interested in anxiety disposition, i.e. TA. Scores for each individual were added to obtain an overall TA score, ranging from a minimum of 20 to a maximum of 80 points.

2.4. Iowa Gambling Task (IGT)

The IGT was originally developed as a card game by Bechara et al. (1994). Here, we used a computerized version of the task, as described previously (Van den Bos et al., 2006). Subjects have to develop a long-term profitable monetary scenario in a situation of uncertainty and a conflict between the chance of encountering an immediate large reward (€100) in two long-term loosing decks (A and B; € − 250 per 10 cards) and the chance of encountering an immediate small reward (€50) in two long-term winning decks (C and D; € + 250 per 10 cards; Bechara et al., 1994). Healthy subjects are more prone to choose advantageous decks C and D over the course of the experiment after about 40 trials (Bechara et al., 1994). No information was given prior to the task on the task features, task duration or the number of trials except for the task objective to raise the budget as much as possible. The task ended after 100 trials.

2.5. Wisconsin Card Sorting Task (WCST)

A computerized version (PEBL Test Battery Version 0.3, http://pebl.sourceforge.net) of the Wisconsin Card Sorting Task (WCST) was used (Heaton et al., 1993). Four different stimulus cards were shown which differed in the number of symbols (1/2/3/4), their color (yellow/green/red/blue) and their shape (square/circle/triangle/star). At the bottom of the screen, a target card was presented, which subjects had to match with one of the four stimulus cards. After giving a response by pressing key '1', '2', '3' or '4', the computer indicated whether the response was 'correct' or 'incorrect' in the center of the screen. Subjects

needed to determine to which rule (shape/color/number) they should attend. After reaching criterion (10 out of 10 responses correct) the rule was changed (reversal).

Before starting the experiment, a brief explanation was given. Subjects were told what the four stimulus cards and the target card indicated, and that the target card was supposed to be matched with one of the stimulus cards by pressing the '1', '2', '3' or '4' key. Subsequently, it was stated that the computer would give immediate feedback ('correct' or 'incorrect'). The subjects were told that the task contained no time limit. The task ended after 128 trials or when subjects completed 9 reversals, whichever came first.

2.6. Cortisol

Saliva for cortisol determination was sampled two times during the experimental procedure. The first sample was taken after a 15 min period of relaxation (see above) and was considered as a baseline, or pre-task, measure. The second sample was taken directly after the WCST, i.e. 10 min after the IGT, which was considered sufficient to use this second sample as a post-task measure (see also Kirschbaum, Pirke, & Hellhamer, 1993). The time span between the first and second cortisol sample was approximately 30 min.

Salivary cortisol samples were taken using a Salivette® (Sarstedt, Nümbrecht, Germany). Participants chewed on the cotton roll for 45–60 s and placed the roll back in the plastic tube. After the experiment, the saliva was extracted from the cotton roll in a centrifuge (4 °C, 3000 rpm, 15 min). Then, 1 ml of saliva was transferred to an Eppendorf vial and stored at −20 °C. The analysis of the samples was done at the laboratory of Endocrinology of the Wilhelmina Children's Hospital of UMC Utrecht (Utrecht, the Netherlands). Saliva cortisol was measured without extraction using an in house competitive radio-immunoassay employing a polyclonal anticortisol–antibody (k7348). [1,2-^{3}H(N)]-Hydrocortisone (Amersham TRK407) was used as a tracer. The lower limit of detection was 1.0 nmol/l and inter-assay variation was 9–5% at 4–37 nmol/l, respectively ($n = 60$). Intra-assay variation was 4% ($n = 10$).

2.7. Behavioral measures

2.7.1. STAI measures

For the STAI questionnaire, scores were extracted for state (SA) and trait anxiety (TA) separately. As we did not find any effects of state anxiety on our IGT, WCST and cortisol measures, we only present TA scores in this paper.

2.7.2. IGT measures

For the IGT, the following two parameters were used for further analysis: the cumulative difference between cards taken from the advantageous decks (C and D) and disadvantageous decks (A and B) and the cumulative amount of money earned, per block of 20 trials.

In addition, the expectancy-valence (EV) model was used to analyze psychological processes underlying IGT performance in more detail (Van den Bos, Homberg, Gijsbers, den Heijer, & Cuppen, 2009). The EV model has been extensively described by Busemeyer and Stout (2002) (see also Yechiam, Busemeyer, Stout, & Bechara, 2005; Yechiam et al., 2008). In short, the EV model decomposes IGT performance in three different psychological processes expressed by different parameters. The first parameter, *w*, reflects the attention of losses versus wins, i.e. quantifies the weighting of losses versus wins. The second parameter, *a*, reflects the extent to which subjects update information to guide their subsequent choices, i.e. it quantifies the extent to which recent information on wins and losses has an impact on subsequent choices. The third parameter, *c*, reflects the extent to which subjects are consistent in their choices, i.e. it quantifies the extent to which choices are guided by expected valences.

2.7.3. WCST measures

For the WCST, the relevant parameters were: the total number of correct responses, the total number of errors, the total number of persevarative errors, the number of trials needed to reach first criterion and the number of trials needed to reach criterion after the first reversal.

2.8. Statistical analysis

All statistical analyses were performed using SPSS 16.0 for Windows and Mackintosh. Based on their TA scores, male and female individuals were categorized as low, medium and high in anxiety. For the low and high anxiety categories, individuals were included that scored >1 standard deviation below or above the mean TA score. All other individuals were included in the medium anxiety group. This categorization method was also used in the study by Miu et al. (2008) that reported effects of TA on IGT performance in a mixed-gender study. To facilitate comparison of our data to the Miu et al. (2008) paper, we chose the same categorization method.

To determine the multi-dimensional structure of TA, we performed a principal component analysis (PCA) on the TA items per gender. PCA was forced into two factors with eigenvalues >1 (see Andrade, Gorenstein, Vieira Filho, Tung, & Artes, 2001) and a Varimax rotation was used to facilitate interpretation of the factor structure. Furthermore, factor scores were saved as variables for further analysis. To determine the effect of TA group on PCA factor scores, a one-way analysis of variance (ANOVA) was used with post hoc least square differences (LSD) test.

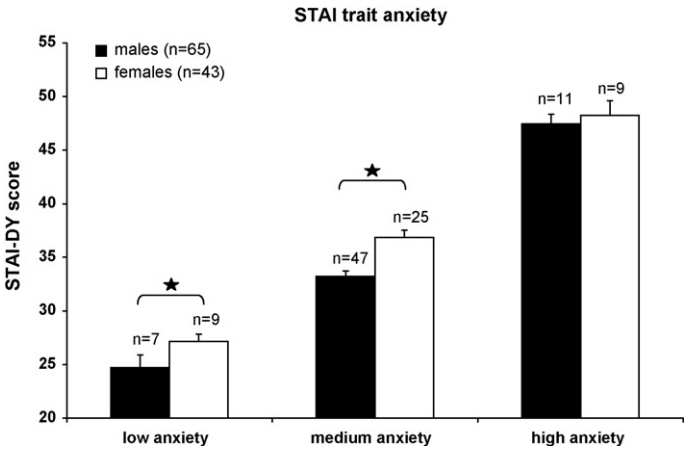

Fig. 1. Overall TA scores from STAI questionnaire per gender and anxiety group. Means ± SEMs are shown, $^*p < 0.05$ for men vs. women. For additional information on statistics see text.

We tested for effects of gender on TA, WCST performance and cortisol using one-way ANOVA, and on IGT performance using a repeated measures ANOVA with trial block as a within-subjects factor and gender as between-subjects factor. Comparisons per trial block were done using one-way ANOVA with gender as factor.

As we found a difference between men and women on the overall TA score, we decided to analyze the differences between TA groups (low, medium and high) on IGT, WCST and cortisol separately for each gender. Effect of TA group on IGT performance was tested using repeated measures with trial block as a within-subjects factor and TA group as between-subjects factor, and subsequent post hoc differences using the least square differences (LSD) test. Effects of TA group on WCST and cortisol were done using a one-way ANOVA with post hoc LSD test.

Significance was set at $p \leq 0.05$. *p*-Values between 0.10 and 0.05 were considered a trend and $p > 0.10$ was considered non-significant (NS). All statistics were two-tailed. For all ANOVAs, η-squared values were provided as an estimation of effect size. Huynh–Feldt epsilon values were used with adjusted degrees of freedom whenever sphericity was violated.

3. Results

3.1. Trait anxiety

3.1.1. Overall TA score

Women tended to show higher overall levels of TA compared to men (men: 34.7 ± 0.9, women: 37.2 ± 1.2, ANOVA: $F_{(1,106)} = 2.97$, $p = 0.09$, $\eta^2 = 0.027$). Fig. 1 shows the levels of TA per gender and per TA group. All categories differed significantly in terms of TA levels in both men ($F_{(2,62)} = 110.742$; $p < 0.0001$, $\eta^2 = 0.781$, post hoc LSD all comparisons: $p < 0.0001$) and women ($F_{(2,40)} = 99.292$; $p < 0.0001$, $\eta^2 = 0.832$, post hoc LSD all comparisons: $p < 0.0001$). Furthermore, higher levels of TA were found in women than men in the low anxiety ($F_{(1,14)} = 6.99$; $p = 0.02$, $\eta^2 = 0.333$) and medium anxiety groups ($F_{(1,70)} = 18.40$; $p < 0.0001$, $\eta^2 = 0.208$).

3.1.2. Principal component analysis

PCA analysis on the STAI TA items revealed a different factor structure in men than in women (Table 1). In men, factor 1 was predominantly comprised of items that relate to negative thoughts and worries, such as "I worry too much over something that really doesn't matter" and "There are thoughts I find hard to let go". Factor 2 was more related to items describing a certain mood or affective state, such as "I feel happy" and "I feel satisfied". In women, the factor structure was opposite to that of men, with factor 1 containing items related to mood and factor 2 containing items related to negative thoughts and worries. Thus, factor 1 in men/factor 2 in women could be labelled as "negative cognition" and factor 2 in men/factor 1 in women could be labelled as "mood" (see also Andrade et al.,

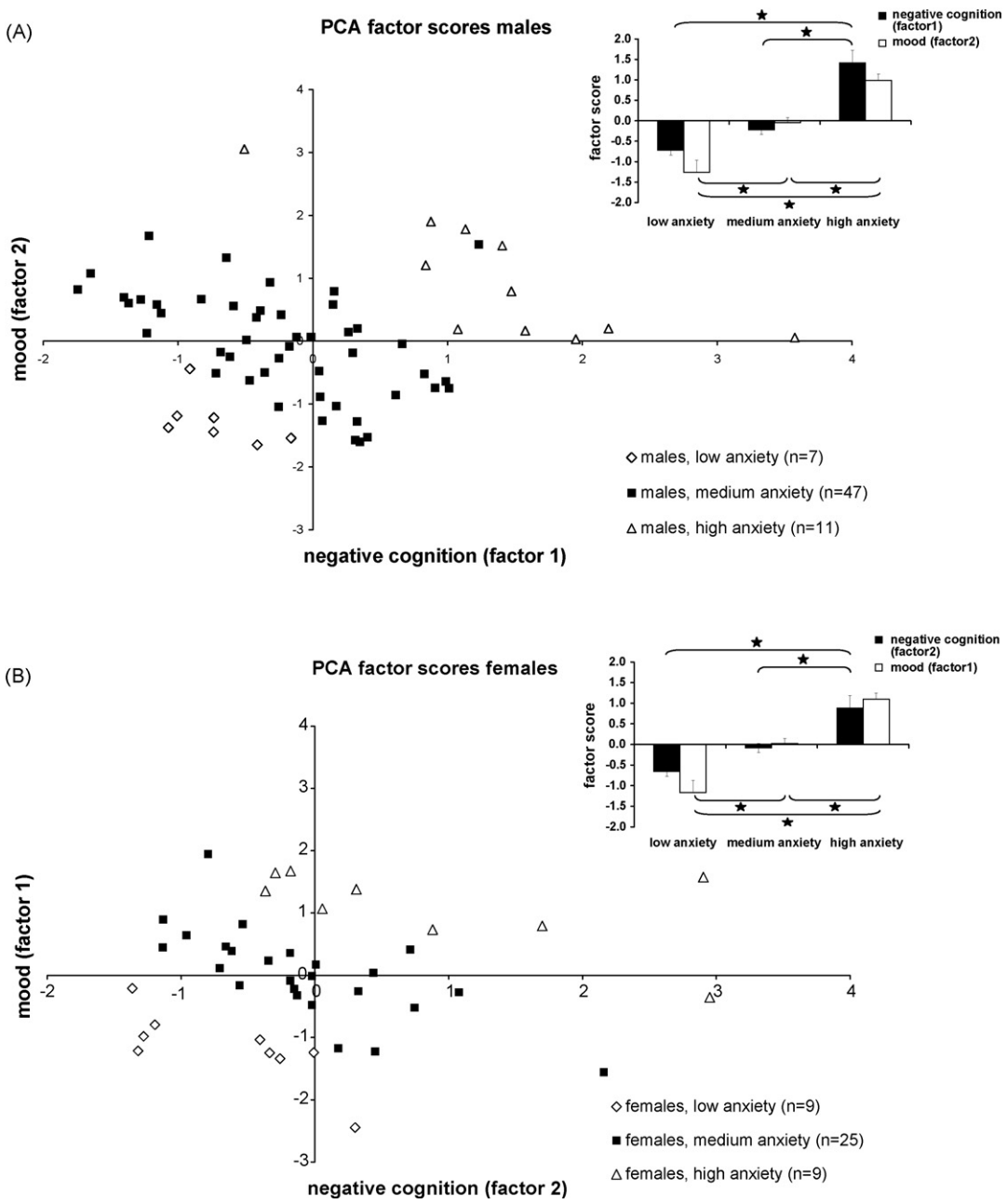

Fig. 2. Factor scores for factor 1 and factor 2 as extracted by principal component analysis (see Table 1). Plots are presented separately for men (panel A) and women (B). Inserts depict the mean (±SEM) factor scores for each TA group on factor 1 and factor 2.

2001). A closer look at the "mood" factor in women revealed that it contains items as "I feel secure" and "I feel comfortable" that did not load onto the "mood" factor in men, indicating a subdimension of "mood" that was particularly relevant for women but not for men.

In Fig. 2A and B, for men and women separately, the individual subjects were plotted against the factors extracted by PCA. Furthermore, the inserts show the mean scores per factor per TA group. TA group significantly affected scores on each factor (see inserts in Fig. 2A and B, one-way ANOVA; men: factor 1, $F_{(2,62)} = 14.22$; $p < 0.0001$, $\eta^2 = 0.439$ and factor 2, $F_{(2,62)} = 16.33$; $p < 0.0001$, $\eta^2 = 0.345$; women: factor 1, $F_{(2,40)} = 24.51$; $p < 0.0001$, $\eta^2 = 0.551$ and factor 2, $F_{(2,40)} = 7.13$; $p < 0.01$, $\eta^2 = 0.263$). In both men and women, all TA groups differed from each other on the "mood" factor (all comparisons, LSD, $p < 0.05$) whereas for the "negative cognition" factor, low and medium anxiety differed from high anxiety but not from each other (men and women, LSD, low vs. medium, $p > 0.10$, NS; low and medium vs. high, $p < 0.05$).

From the scatterplots in Fig. 2A and B it becomes clear that in men, high anxiety individuals are differentiated from medium and low anxiety mostly by factor 1/"negative cognition". In women, the dissociation between TA groups is more equally distributed across the two factors.

Overall, the PCA data indicate that TA consists of a "negative cognition" dimension and a "mood" dimension that are of different relative importance to the overall TA score in men and women.

3.2. Iowa Gambling Task

3.2.1. Subjects excluded

For analysis of the IGT data, data of 2 men and 3 women were excluded as they indicated to have had knowledge of the principles of the task.

Table 1
Principal component analysis on STAI TA items per gender. Only items with loading >0.6 are included. Item descriptions (directly translated from Dutch when there was no English equivalent in the original STAI questionnaire (Spielberger, 1983)): 21. "I feel pleasant", 23. "I feel satisfied", 24. "I have difficulties dealing with misfortunes", 27. "I am calm, cool and collected", 29. "I worry too much over something that really doesn't matter", 30. "I am happy", 31. "I have disturbing thoughts", 32. "I lack self-confidence", 33. "I feel secure", 34. "I feel comfortable", 35. "I am a steady person", 36. "I am content", 37. "There are thoughts I find hard to let go", 38. "I take disappointments so keenly that I can't put them out of my mind", and 40. "I get in a state of tension or turmoil as I think over my recent concerns".

STAI item	Males		Females	
	Factor 1	Factor 2	Factor 1	Factor 2
21. "pleasant"		0.788		
23. "feel satisfied"		0.791	0.735	
24. "misfortunes"				0.647
27. "calm, cool, collected"			0.733	
29. "worry too much"	0.624			
30. "happy"		0.747	0.680	
31. "disturbing thoughts"	0.707			0.724
32. "lack self-confidence"				0.724
33. "secure"			0.676	
34. "comfortable"			0.708	
35. "steady"			0.693	
36. "am satisfied"		0.771	0.785	
37. "thoughts let go"	0.811			
38. "disappointments"	0.761			0.638
40. "concerns"	0.702			0.738
% variance explained	32.1	10.6	38.1	10.2

3.2.2. Advantageous–disadvantageous choices

Men tended to outperform women as reflected by a steeper increase in the cumulative number of cards chosen from the advantageous (CD) minus the advantageous decks (AB) (ANOVA, block × gender; $F_{(4,142.4)} = 2.33$; $p = 0.10$, $\eta^2 = 0.023$). Note that data are not shown here, but for an illustration of the gender difference in IGT performance: compare the trajectories of male and female medium TA subjects from Fig. 3A and B.

In men, TA group differed with respect to the cumulative CD − AB choices (Fig. 3A, ANOVA, between-subjects effect of TA group: $F_{(2,60)} = 3.06$; $p = 0.05$, $\eta^2 = 0.092$). Both high anxiety (LSD, block 21–40 and 81–100, $p < 0.05$) and low anxiety (LSD, block 41–60: $p < 0.05$; block 81–100: $p < 0.10$) men performed worse on the IGT compared to medium anxiety subjects. The differential effect of TA group was most pronounced in the beginning of the test.

It is clear from Fig. 3A that by the end of the task the final performance of both high and low anxiety men did not exceed chance level (CD − AB = 0, meaning as much choices from disadvantageous as from advantageous decks), whereas medium anxiety subjects perform well above chance.

Repeated measures ANOVA did not reveal a significant between-subjects effect of TA on IGT performance in women. However, as low and medium TA women showed very similar IGT performance (Fig. 3B), we conducted a planned contrast comparison with high TA women versus low and medium TA women. This analysis revealed a nearly significant block × TA group effect in women ($F_{(4,79.7)} = 2.956$, $p = 0.055$, $\eta^2 = 0.072$), suggesting that the IGT performance trajectory of high anxiety women differed from their low and medium anxiety counterparts. Fig. 3B shows the IGT performance for low, medium and high anxiety women. As the task progressed, high anxiety women chose less of the advantageous decks than medium and low anxiety subjects (LSD, block 41–60, $p < 0.10$ and block 61–80, $p < 0.05$). Notably, the effect of TA in women appeared at a later stage than in men. The final performance of high anxiety women did not exceed chance levels, in contrast to medium and low anxiety women. Furthermore, in contrast to men, low anxiety women did not differ from medium subjects.

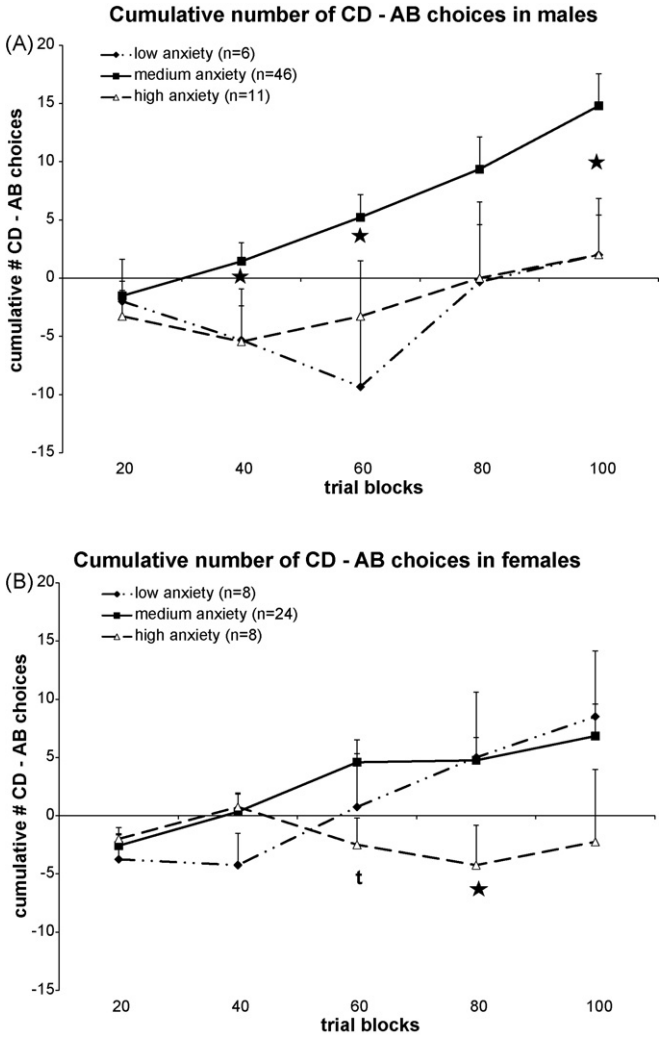

Fig. 3. Cumulative number of advantageous (CD)–disadvantageous (AB) choices in the IGT for low, medium and high anxiety subjects in men (panel A) and women (panel B). Means ± SEMs are shown, $^*p < 0.05$ for differences between TA groups. For additional information on statistics see text.

3.2.3. Money earned

The cumulative amount of money earned followed a different trajectory in men than in women (ANOVA, block × gender; $F_{(4,404)} = 3.64$; $p = 0.01$), with a higher initial budget in women (block 20, $p < 0.05$), but men earned more money in the second phase of the test (block 60, $p < 0.05$). Note that data are not shown here, but for an illustration of the gender difference in money earned: compare the trajectories of male and female medium TA subjects from Fig. 4A and B.

In men, there was a significant difference between TA groups on the total amount of money earned at trial 100 (Fig. 4A, ANOVA, TA group: $F_{(2,62)} = 3.23$; $p = 0.05$), with a lower amount of money earned for low anxiety men compared to medium anxiety men (LSD, $p < 0.05$). In women, no effect was found of TA group on the amount of money earned (Fig. 4B).

3.2.4. Expectancy-valence model

No effects of either gender (ANOVA, all parameters, $p > 0.10$, NS) or TA group (ANOVA, all parameters, $p > 0.10$) were found.

Table 2
Results from the Wisconsin Card Sorting Task per gender and anxiety group. *# correct* = the number of correct responses, *# tot. errors* = the total number of incorrect responses, *# pers. errors* = the number of perseverative errors, *1st criterion* = the number of trials needed to reach first criterion, and *1st reversal* = the numbers of trials needed to reach criterion after the first reversal. Means ± SEMs are shown.

	n	*# correct*	*# tot. errors*	*# pers. errors*	*1st criterion*	*1st reversal*
Males (all)	62	94.6 (1.3)	30.8 (1.6)	20.5 (1.0)	14.2 (0.8)	22.8 (2.0)
Low anxiety	7	94.1 (3.5)	29.9 (5.0)	20.9 (4.4)	13.9 (1.8)	20.0 (4.6)
Medium anxiety	44	95.5 (1.6)	29.5 (1.8)	19.5 (1.1)	14.8 (1.0)	23.5 (2.2)
High anxiety	11	91.2 (3.6)	36.4 (3.8)	24.5 (2.4)	12.2 (0.6)	22.2 (6.5)
Females (all)	42	94.8 (2.2)	31.8 (2.3)	20.2 (1.6)	17.2 (2.7)	25.1 (2.5)
Low anxiety	8	92.8 (8.1)	33.9 (8.5)	25.6 (7.0)	12.5(2.5)	29.4 (11.1)
Medium anxiety	25	96.5 (2.0)	30.4 (2.1)	18.4 (1.2)	19.6 (4.2)	23.6 (2.2)
High anxiety	9	92.0 (6.2)	33.9 (6.9)	20.4 (3.0)	14.8 (4.5)	25.3 (3.9)

3.3. Wisconsin Card Sorting Task

For analysis of the WCST data, 3 men and 1 woman were excluded as they indicated to have had knowledge of the principles of the task.

Table 2 lists the results of the WCST per gender and TA group. No effect was found of either gender (ANOVA, all parameters, $p > 0.10$, NS) or TA group (ANOVA, all parameters, $p > 0.10$, NS). Thus, gender and trait anxiety did not influence performance on executive functioning as measured by the WCST.

3.4. Cortisol

To determine a possible influence of anticipatory stress on decision-making, we analyzed cortisol before (CORT1) and after the test procedure (CORT2, see Table 3 for results). In general, there was a decrease in cortisol levels at the end of the test procedure compared to the first sample, indicating that the test procedure was not particularly stressful. We found no gender differences in cortisol levels (ANOVA, between-subjects effect of gender, $p > 0.10$, NS). In men, but not in women, low anxiety subjects tended to have lower basal cortisol levels than medium and high anxiety subjects (ANOVA, $F_{(2,62)} = 3.01$, $p = 0.06$; LSD low vs. medium and high, $p < 0.05$). No effect of TA group was found in either gender on the second cortisol sample.

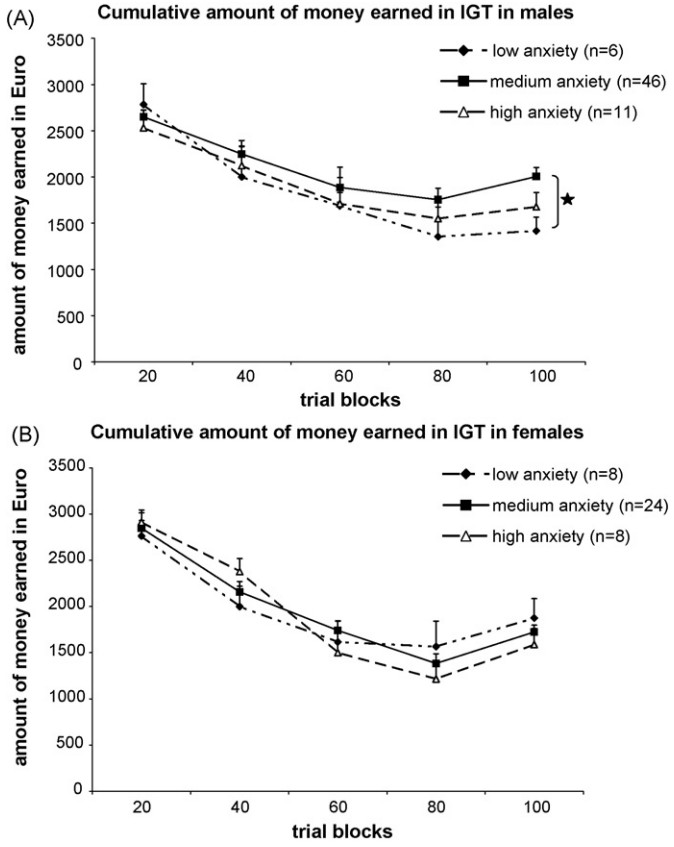

Fig. 4. Cumulative amount of money earned in the IGT for low, medium and high anxiety subjects in men (panel A) and women (panel B). Means ± SEMs are shown, $^{*}p < 0.05$ for differences between TA groups. For additional information on statistics see text.

4. Discussion

4.1. Main findings

We investigated the interaction between trait anxiety (TA) and complex decision-making in relation to gender. The study yielded two main results. Firstly, independent of gender, high levels of TA resulted in a poor performance in decision-making (IGT performance). Secondly, gender-specific effects were observed: in men, both low and high anxiety individuals showed an impaired IGT performance, whereas in women a comparable effect was only found in high anxiety subjects. Furthermore, in men, the effect of anxiety on decision-making already became visible during the first part of the task, i.e. the exploration phase. In women, high anxiety affected performance during the second part of the task, i.e. the exploitation phase.

4.2. Effects of anxiety on decision-making across genders

Our finding of an impaired IGT performance in healthy but high TA subjects is in agreement with an earlier study by Miu et al. (2008) who reported similar findings in a mixed-gender study. High TA subjects choose more disadvantageous cards and seem unable to develop as quickly a profitable long-term strategy. It should be noted, that the mean scores of our low, medium and high TA groups were similar to scores obtained with different categorization methods (quartiles; Zimmerman-Viehoff, Weber, Merswolken, Rudat & Deter, 2008). Furthermore, the mean TA scores of our

Table 3
Salivary cortisol levels in nmol/l measured before (*CORT1*) and after (*CORT2*) the test procedure per gender and anxiety group. Means ± SEMs are shown.

	n	CORT1	CORT2
Males (all)	65	11.7 (0.6)	10.8 (0.9)
Low anxiety	7	8.4 (1.0)*	8.8 (1.2)
Medium anxiety	47	12.5 (0.7)	11.5 (1.3)
High anxiety	11	10.3 (1.4)	9.1 (1.0)
Females (all)	43	11.0 (0.6)	10.0 (0.5)
Low anxiety	9	13.0 (2.3)	11.5 (1.9)
Medium anxiety	25	10.2 (0.5)	9.3 (0.4)
High anxiety	9	11.4 (1.6)	10.4 (1.2)

* $p < 0.05$ for low anxiety vs. medium and high anxiety.

male and female medium TA groups are similar to the normative data of a larger sample of the Dutch population as stated in the Dutch manual of the STAI (Van der Ploeg, 2000). This indicates that our sample represents the distribution of TA in the general (Dutch) population. However, the high TA group scores of the Miu et al. (2008) and Stein, Simmons, Feinstein, and Paulus (2007) studies are higher than what we and Zimmerman-Viehoff et al. (2008) report. In fact, the means of these high TA group scores are above the mean TA score reported for psychiatric patients (mean = 52.0, SD = 12.4, Van der Ploeg, 2000). Interestingly, our findings are similar to what Miu et al. (2008) reported for their high TA group, i.e. high anxiety impairs IGT performance. This suggests that the effects of high TA on decision-making are already found at subclinical TA levels (our data) but also extend to clinical TA levels.

Importantly, these effects were not secondary to potentially confounding factors. For, in contrast to an earlier hypothesis by Miu et al. (2008) saliva cortisol measurements in the present study indicate that the effect of anxiety on decision-making cannot be explained by stress related to state-dependent factors on the day of testing. In line with this, we did not find an effect of state anxiety on any of the behavioural and physiological measures in this study (unpublished data).

Furthermore, we did not find an effect of TA on executive functioning as measured by the WCST. This suggests that the IGT, an emotional decision-making task, is more sensitive to the effects of TA than the WCST, a task that measures cognitive flexibility and rule learning. It also indicates, that in our sample, differences in IGT performance could not be explained by underlying differences in WCST performance.

4.3. Gender-specific effects on the interaction between anxiety and decision-making: men

To the best of our knowledge this is the first study to show that men and women differ with respect to the influence of TA on IGT performance. Specifically in men, both low and high TA subjects show a less successful decision-making performance than medium TA subjects did. In more detail, we observed that in men TA affects IGT performance already in the beginning of the task, during the exploration phase. We hypothesize that this effect is mainly due to a higher emotional response to the negative events (losses) occurring during the exploration phase.

Factor analysis showed that trait anxiety in the here tested subjects was composed of two main dimensions: PCA revealed a dimension related to negative thoughts and worries, including STAI items such as "I worry too much over something that really doesn't matter" and "There are thoughts I find hard to let go". This dimension was independent of the second one, which related to mood and affective state, including STAI items such as "I feel happy" and "I feel satisfied". This general factor structure is in agreement with a study by Andrade et al. (2001) in a Brazilian sample of college students.

In the present study, the first dimension of negative thoughts and worries was predominant in men, especially in high TA men. We therefore suggest that high TA men are characterised by a too strong emotional reactivity which is mainly expressed at the beginning of the IGT. As a consequence of this characteristic, high TA men further show an incorrect prediction of the long-term payoff of the decks. Probably due to their unaffected good cognitive control system and goal-directedness, previously found in men (Bolla et al., 2004; Reavis & Overman, 2001; Van den Bos et al., 2007), the disadvantageous choice strategy is maintained throughout the task, resulting in a less successful accomplishment of the task.

4.4. Gender-specific effects on the interaction between anxiety and decision-making: women

High TA female subjects performed poorly on the IGT compared to both their low and medium TA counterparts. In women the effect of high TA emerged in the second part of the test, the exploitation phase. Thus, the IGT performance starts off similarly in all female subjects, but as the task progresses, high TA subjects fail to maintain their performance and start to increase the number of disadvantageous choices. The differential effect of TA on decision-making in women compared to men cannot be explained by gender differences in anxiety levels per se, as TA scores for the high TA groups were similar in men and women.

In general, men outperform women on the IGT by showing a more goal-direct choice pattern during the exploitation phase (present study, Bolla et al., 2004; Reavis & Overman, 2001; Van den Bos et al., 2007). The IGT performance of women in general suggests that their decision-making strategy is more strongly than in men dominated by ongoing exploration and gathering of information before an actual choice strategy is established and maintained. It was argued that a weaker cognitive control system could account for the exploratory choice strategy of women (Van den Bos et al., 2007).

Interestingly, in women the dominant factor underlying high TA was mood or affective state, more specifically, to a feeling of insecurity and discomfort. Thus, in contrast to their high TA male counterparts, high anxiety women obviously tend to strongly doubt their choices, resulting in maintained exploratory behaviour as a disadvantageous strategy. Thus, the impaired IGT performance in high TA women may be the result of further weakening of the cognitive control system's influence on choice behavior.

4.5. Low TA impairs decision-making in men, but not women

Specifically in men, TA subjects showed impaired decision-making compared to medium TA subjects as well, just like high TA subjects. This finding seems to contrast the results of the study by Miu et al. (2008), who reported a superior performance of low TA subjects compared to high TA individuals. However, the study by Miu and colleagues was performed in a mixed-gender sample with the low TA subject group mainly consisting of women: 5 women versus 3 men, a sample size that was too small to allow for a gender-specific analysis.

The relationship between TA and decision-making in men thus follows an inverted U-shaped curve. This curve may be reminiscent of the Yerkes-Dodson effect (1908) that described an inverted U-shaped relationship between the level of arousal and cognitive performance in mice. Also, inverted U-shaped curve has been reported for the relationship between TA and visuomotor integration (Colzato, Kool, & Hommel, 2008). Apparently, medium levels of TA may be optimal for information processing in both emotional- and non-emotional-tasks in men.

We hypothesize that in contrast to the emotional hyperreactivity related to high TA as suggested above, low TA men in the present study showed a poor IGT performance due to an emotional hyporeactivity, reflected by low scores on the anxiety dimension of negative thoughts and worries. This emotional hyporeactivity would then result in an underestimation of the high and frequent losses in decks A and B. In fact, when the individual decks are considered (data not shown), the choice pattern of low anxiety men may be indicative of increased risk-taking. This is also supported by our finding that low TA men had lower basal cortisol levels; low basal cortisol has been associated with increased risk-taking (Van Honk, Schutter, Hermans, & Putman, 2003). Furthermore, in a recent study it was found that poor IGT performance was related to both increased novelty-seeking and risk-taking in

male subjects carrying a specific variant of the gene coding for the dopamine D4 receptor (L-DRD4 variant; Roussos, Giakoumaki, & Bitsios, 2009). Interestingly, L-DRD4 subjects also showed an hyporeactivity to unconditioned emotional stimuli, suggesting an association between emotional reactivity, risk-taking and decision-making that is modulated by dopamine.

In our study, we did not find impaired IGT performance in low TA women, indicating that low TA men and women differ in their personality profiles, with a less prominent role of risk-taking or novelty-seeking behaviour in low TA women than in low TA men. In fact, the characteristic IGT-profile of low TA men, together with the findings from the L-DRD4 subjects touch upon a very relevant issue, namely that low-TA men may be at a higher risk to develop psychopathologies such as addiction. As there are very few studies that systematically address gender-specific effects in the relation between emotionality, risk-taking behaviour and decision-making, the underlying mechanisms remain poorly understood and should be subject of future research.

We are currently performing studies using specific risk-taking tasks to elucidate whether risk-taking indeed is the underlying psychological construct of the poor decision-making in low TA men and preliminary data show that low TA men are overrepresented in the group of subjects that display poor decision-making and high risk-taking.

4.6. Neurobiological mechanisms underlying IGT performance—conclusions from gender differences

The mechanism underlying the poor IGT performance in highly anxious individuals may be explained by common neural substrates that mediate the interaction between TA and decision-making. High TA is associated with enhanced AMY and OFC activation (Bishop et al., 2004; Etkin et al., 2004; Grachev & Apkarian, 2000; Simpson et al., 2001) and altered activity of the ACC and dorsolateral PFC (Bishop et al., 2004; Bishop, 2008; Paulus et al., 2004; Simmons et al., 2008), areas that are of crucial importance in decision-making as well (Bechara et al., 1999; Bolla et al., 2004; Brand et al., 2006; Doya, 2008; Ernst et al., 2002; Ridderinkhof, Ulsperger, Crone, & Nieuwenhuis, 2004; Van den Bos et al., 2007). More specifically, it has been suggested that IGT-exploration and IGT-exploitation, respectively, are processed by specific brain areas (Van den Bos et al., 2007): the exploration phase is mainly mediated by the amygdala (affective labelling of the cards; Bechara et al., 1999) and ventral striatum (mediation of responses to and anticipation of rewards; Knutson, Fong, Adams, Varner, & Hommer, 2001) and its projections to the OFC to integrate the information of individual card valence to form a notion of the long-term valence of each deck (Bechara et al., 1999). As the task progresses and a preference for the advantageous decks is emerging, the ACC, lPFC and dorsal striatum are recruited to engage in cognitive control of the once established choice in order to maintain and exploit this strategy to secure long-term pay-off (Bush, Luu, & Posner, 2000; Ernst et al., 2002; McClure, Laibson, Loewenstein, & Cohen, 2004; Pezawas et al., 2005; Ridderinkhof et al., 2004). An important role for the ACC is thought to be the intermediate between the "ventral loop", important for the exploration phase, and the "dorsolateral" loop, important for the exploitation phase. The ACC engages in cognitive control by conflict monitoring and consequent signalling to the lPFC when control should be enhanced (Ridderinkhof et al., 2004). At the same time, ACC projections to the amygdala may be involved in inhibitory feedback to diminish affective signalling (Pezawas et al., 2005), in order to sustain cognitive control over the once established choice. The latter may be especially crucial in the IGT as all options, including the advantageous ones, have a certain probability of a negative outcome. However, in the second phase of the task, a response to these immediate negative outcomes should be withheld in favour of the long-term pay-off. Considering the overlapping neural substrates of TA and decision-making, anxiety may exerts its influence on decision-making performance both on the level of emotional reactivity and affective labelling, involving mainly the "ventral" loop, and on the level of cognitive control, involving mainly the ACC and the "dorsolateral" loop.

Considering our present findings, we propose that gender differentiates between these neural pathways. As IGT performance in males was affected already during exploration, it is likely that in men, anxiety exerts its influence predominantly in the "ventral" loop, i.e. the OFC–AMY–vSTR connection. In favour of this hypothesis, it was found that in a male-biased sample, high TA was associated with increased OFC activation (Grachev & Apkarian, 2000). Furthermore, in an implicit learning task, men outperformed women, but also showed stronger activation of the OFC, AMY and vSTR (Hoeft, Watson, Kesler, Bettinger, & Reiss, 2008), structures involved in the early phase of the IGT, a phase primarily affected by TA in men.

In women, however, exploitation was affected rather than exploration and thus anxiety mainly alters decision-making at the level of cognitive control, mediated by the ACC and "dorsolateral" loop (lPFC and dSTR). In support of this hypothesis, female-biased studies showed an altered activation of the ACC in relation to TA (Bishop et al., 2004; Paulus et al., 2004; Simmons et al., 2008). In support, women did not recruit the dlPFC during IGT, a structure that is part of the cognitive control system (Bolla et al., 2004).

To further elucidate the neural pathways underlying the interaction between TA and decision-making, we have recently developed a translational rodent model of the IGT (Homberg et al., 2008) that enables us to study decision-making in rats and mice in parallel to our human studies. This research is aimed at directly manipulating the brain areas thought to be involved in anxiety and decision-making in rodents (Kalisch et al., 2004; Pais-Vieira, Lima, & Galhardo, 2007). Further, we will complement our animal research by developing behavioural tests for humans to more specifically address the gender-specific endophenotypes of anxiety found in the present study, i.e. high emotional reactivity in men and diminished cognitive control in women.

4.7. Conclusions

Trait anxiety was found to gender specifically affect decision-making in healthy human subjects. We suggest that TA effects in men are mainly expressed at the level of emotional reactivity, while the impact of TA in women can be found predominantly at the level of cognitive control. Our findings underscore the importance of studying the behavioural and neurobiological processes underlying trait anxiety differentially in both men and women. Although it is known that anxiety is not a unitary concept but consists of different endophenotypes, rarely any attention has been spent to the question, whether gender-specific endophenotypes of TA may result in specific (dysfunctional) decision-making processes. Such knowledge may refine diagnostic as well as treatment strategies for human anxiety patients.

Conflict of interest

None declared.

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